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Opinion Article

The Crucial Role of Transporters in Drug Disposition and Metabolism

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DESCRIPTION

The field of pharmacology has made significant makes progress in understanding how drugs are absorbed, distributed, metabolized and excreted within the human body, a process collectively referred to as drug disposition. This complex interplay of physiological processes is vital in determining a drug's efficacy and safety. While the focus has historically been on drug-metabolizing enzymes, the role of transporters in drug disposition and metabolism has gained increasing recognition in recent years. Transporters, specifically membrane-bound proteins that facilitate the movement of molecules across biological membranes, has a main role in drug absorption, distribution and excretion.

Drug absorption

The journey of a drug begins with its administration, whether through oral ingestion, injection or other routes. For orally administered drugs, the Gastro Intestinal (GI) tract is the initial battleground where absorption occurs. Transporters present in the GI tract are responsible for moving drugs from the intestinal lumen into the bloodstream. The primary transporters involved in drug absorption are flow transporters like P-Glyco Protein (P-GP), which are located on the apical membrane of intestinal epithelial cells. P-gp actively pumps drugs back into the GI lumen by limiting their absorption.

Drug distribution

Once absorbed into the bloodstream, drugs must be distributed to their target tissues. Transporters found in various organs and tissues, such as the liver, kidneys and brain has a significant role in this process. In the liver, hepatic transporters like Organic Anion Transporting Polypeptides (OATPs) and Organic Cation Transporters (OCTs) are responsible for transporting drugs from the blood into hepatocytes. In the kidneys, transporters like Organic Anion Transporters (OATs) and Organic Cation Transporters (OCTs) facilitate the secretion of drugs into urine by contributing to drug elimination. Additionally, transporters in the Blood-Brain Barrier (BBB), such as P-gp and Breast Cancer Resistance Protein (BCRP), regulate the passage of drugs into the brain. This selective barrier limits the entry of potentially harmful substances while influencing the effectiveness of drugs targeting the central nervous system.

Drug metabolism

Drug metabolism is a critical aspect of drug disposition and involves the chemical alteration of drugs to make them more water-soluble and easier to excrete. While drug-metabolizing enzymes like cytochrome P450s are well-known for their role in this process, transporters are equally indispensable. For example, hepatic transporters can facilitate the uptake of drugs and their metabolites into hepatocytes, where they can be further metabolized. In some cases, transporters can transport drugs out of hepatocytes, preventing them from undergoing extensive metabolism. This balance between transporters and metabolizing enzymes influences a drug's pharmacokinetics and therapeutic effects.

Drug excretion

Elimination of drugs from the body is primarily achieved through renal excretion, where transporters in the kidneys has a main role. Renal transporters, including OATs, OCTs, and Multidrug Resistance-Associated Proteins (MRPs), are responsible for moving drugs and their metabolites from the bloodstream into urine. This process helps maintain drug concentration within a therapeutic window and prevents drug accumulation, which could lead to toxicity. Dysfunction or inhibition of these renal transporters can result in altered drug excretion and potential adverse effects.

Transporter-drug interactions

Understanding transporter-drug interactions is crucial for predicting and managing potential drug to drug interactions and optimizing drug therapy. Some drugs can inhibit or induce transporter activity, leading to altered drug disposition. For example, a drug that inhibits P-gp may increase the absorption of co-administered drugs that are P-gp substrates, potentially

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leading to drug toxicity. On the other hand, drugs that induce transporter expression can increase the clearance of co-administered drugs, reducing their efficacy. Identifying and predicting such interactions is essential for patient safety and effective drug therapy.

Pharmacogenomics and transporters

Individual genetic variability in transporter expression and function can significantly impact drug disposition and response. Pharmacogenomics studies have identified genetic polymorphisms that affect transporter activity, leading to inter-individual differences in drug pharmacokinetics. For instance, genetic variations in the OATP1B1 transporter can influence the pharmacokinetics of statin drugs, which are commonly used to lower cholesterol levels. Pharmacogenomics testing can help personalize drug therapy by adapting drug selection and dosing to an individual's genetic profile, improving treatment outcomes while minimizing adverse effects.

Transporters in drug development

Recognizing the importance of transporters in drug disposition and metabolism, regulatory agencies such as the U.S. Food and Drug Administration (FDA) now require the evaluation of transporter-related drug interactions during the drug development process. Additionally, the incorporation of transporter data into Physiologically Based Pharmacokinetic (PBPK) modelling has become an essential tool for predicting drug behavior in humans and guiding dosing recommendations.